

REMARKS

Claims 1, 5-7, 9-18, 20-26, 33, 35-39, 41 and 43-46 are in the application. Claims 1, 2, 5-7, 9, 18, 20-26, 33 and 35-41 remain rejected under 35 U.S.C. §112, first paragraph. Claims 7 and 41 remain rejected under 35 U.S.C. §112, second paragraph. Claims 1, 5-7, 10-12, 14, 16, 39-40, 43, 44, and 46 remain rejected under 35 U.S.C. §102(b). Claims 1, 7, 10, 11, 15, 39, 41 and 44 remain rejected under 35 U.S.C. §103(a). Claims 1, 10, 12, 13, 15, 16, 39 and 44-46 are rejected under 35 U.S.C. §103(a). Entry of the amendment, reconsideration of the rejection, and allowance of all pending claims are requested.

The Amendment

Claims 1, 9, 18, 33, 38 and 39 have been amended. The amended claims are supported by the application as filed. Claim 47 has been added. The new claim is supported by the application as filed. Claims 6, 7 and 41 have been canceled. Entry of the amendment is respectfully requested.

Rejections Under 35 U.S.C. §112

Claims 1, 2, 7, and 39-41 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. With regard to this rejection, the Examiner asserts that the specification does not disclose any promoter sequences of HSP28, HSP72 or HSP73.

Claims 2 and 40 were canceled in the amendment filed on December 28, 2000 as entered by the Examiner. Claims 1 and 39 have been amended to specify that the heat shock promoter is selected from the group consisting of HSP70, HSP90, HSP60, HSP27, HSP25, and ubiquitin promoters. In light of this amendment, the rejection is moot. Claims 1 and 39 have further been amended to remove specific temperature conditions. Support for the amendment can be found on page 4, lines 15-20 and page 33, lines 18-20 of the specification. Claims 7 and 41 have been canceled.

In light of the amendment, Applicants respectfully request that the rejection of claims 1 and 39 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 1, 5-7, 9, 18, 20-26, 33 and 35-38 are rejected under 35 U.S.C. §112, first paragraph. Applicants have amended claims 1, 18, 33 and 38 to specify that the heat shock promoter is selected from the group consisting of HSP70, HSP90, HSP60, HSP27, HSP25, and ubiquitin promoters. In light of this amendment, the rejection is moot. Claims 1, 18, 33 and 38 have further been amended to remove specific temperature conditions. Support for this amendment can be found in the specification as indicated above (*supra*). Claim 9 has been amended to delete reference to tat while claim 47 has been added to claim tat. Claims 5 and 9 depend on claim 1. Claims 6 and 7 have been canceled. Claims 20-26 depend directly or indirectly on claim 18. Claims 35-37 depend directly or indirectly on claim 33.

In light of the amendment, Applicants respectfully request that the rejection of claims 1, 5, 9, 18, 20-26, 33 and 35-38 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. §102

Claims 1, 5-7, 10-12, 14, 16, 39-40, 43, 44, and 46 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bromley *et al.* (EP 0299127, 1989).

The rejection of claims 1, 5, 10-12, 14, 16, 39, 43, 44, and 46 is respectfully traversed.

The Examiner asserts that Applicants' argument that Bromley *et al.* do not disclose or teach a construct where the hybrid genes are carried on one vector and therefore do not enable one skilled in the art to make the same is not persuasive. The Examiner further asserts that Bromley *et al.* teach that hybrid genes can be part of one or separate vectors, referring Applicants to pages 3-6. Applicants reiterate that Bromley *et al.* do not teach that hybrid genes can be carried on a single vector; no data was presented suggesting that Bromley *et al.* knew how to construct such a dual gene vector. Although Bromley *et al.* claim a method where hybrid genes are carried on one vector (see claim 5, EP 0299127), they have not enabled the same. Applicants refer the Examiner to the declaration of Dr. David T. Harris. In this declaration, Dr. Harris explains why dual gene vectors are difficult to construct. Further, Dr. Harris states that the inventors were the first to publish the successful construction of a dual gene expression vector that facilitates the simultaneous expression of two genes (Tsang *et al.* January 1997 BioTechniques 22:68; see attached copy of article). The inventors accomplished this by developing a new cloning system that allowed any two pieces of DNA to be joined together with more ease and in less time than previously possible (Tsang *et al.* January 1996 BioTechniques 20:51-52; see attached copy of article). As stated in the declaration, it is known to Applicants that 10 years after

Bromley *et al.* had filed the PCT application Bromley *et al.* had still not constructed a single DNA vector with hybrid genes as claimed in EP 0299127. Applicants respectfully assert that Bromley *et al.* were not able to construct, thus enable, a dual gene vector such as the one disclosed in the instant invention at the time of filing of EP 0299127. Undue experimentation would have been required in order to use Bromley *et al.*'s disclosure to construct dual gene vectors prior to Applicants' invention. Bromley *et al.* provided merely an invitation to those of skill in the art to construct such dual gene vectors. Applicants refer the Examiner to MPEP 2164.01(a) where undue experimentation factors are discussed. Further, MPEP 2164.06(b) (Examples of Enablement Issues – Chemical Cases [R-1]) states the following:

“...In *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999), the court held that claims in two patents directed to genetic antisense technology (which aims to control gene expression in a particular organism), were invalid because the breadth of enablement was not commensurate in scope with the claims. Both specifications disclosed applying antisense technology in regulating three genes in *E. coli*. **Despite the limited disclosures, the specification asserted that the “[t]he practices of this invention are generally applicable with respect to any organism containing genetic material which is capable of being expressed...such as bacteria, yeast, and other cellular organisms.”**...Ultimately, the court relied on the fact that (1) the amount of direction presented and the number of working examples provided in the specification were very narrow compared to the wide breadth of the claims at issue...Thus, **the teachings set forth in the specification provided no more than a “plan” or “invitation” for those of skill in the art to experiment using the technology in other types of cells.** [bold emphasis added]

The Examiner argues that Bromley *et al.* clearly teach the components of the vector of the instant invention and the method of using the vector. Applicants point out that the vectors of the instant invention are inducible and regulatable and produce higher levels of

gene expression than any expression vector reported to date. More specifically, the vectors f12 and 007 (derived by modifying vectors X14 and Y15) (see Tables 3 and 4 in the specification on page 63 and 67, respectively) produce gene expression levels that are significantly higher than the current standard, the CMV promoter (L27). There are no vectors currently available that can reach the levels of expression achieved by X14, Y15, f12 and 007. Conversely, Bromley *et al.*, even with their single gene vectors, do not teach higher levels of gene expression, rather they teach longer durations of expression (see page 9, line 25, claim 1). In light of the declaration and comments supplied by Applicants it should be clear that Bromley *et al.* fail to teach, either expressly or inherently, the vectors of the instant invention. Thus, Applicants respectfully request that the rejection of claims 1, 5, 10-12, 14, 16, 39, 43, 44, and 46 under 35 U.S.C. §102(b) be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 1, 10, 12, 13, 15, 16, 39 and 44-46 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bromley *et al.*, taken with Gage *et al.*

The rejection of claims 1, 10, 12, 13, 15, 16, 39 and 44-46 is respectfully traversed.

Claims 1 and 39 have been amended (*supra*).

The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the expression construct of Gage *et al.* by substituting the inducible promoter of Gage *et al.* with the inducible heat shock promoter of Bromley *et al.* in view of the advantages of the promoter taught by Bromley *et al.*, *e.g.*, a substantially prolonged time of expression induced by a single heat activation

cycle which would minimize cell growth inhibition and subsequent cell death which would be observed with multiple cycles of heat activation.

As already discussed with respect to the 35 U.S.C. § 102(b) rejection, Bromley *et al.* were not able to construct a dual gene vector such as the one disclosed in the instant invention at the time of filing of EP 0299127 (*supra*). As pointed out by the Examiner, Gage *et al.* do not teach using a heat shock promoter in the expression construct. Rather, Gage *et al.* disclose a vector that is regulatable by the addition of tetracycline (see column 2, lines 6-7). Thus, there was no motivation whatsoever to combine Bromley *et al.* and Gage *et al.* because there is no motivation in either the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine them (MPEP 2143.01). Applicants assert that there is simply no motivation to substitute the inducible promoter of Gage *et al.* with the inducible heat shock promoter of Bromley *et al.* in view of the fact that not even Bromley *et al.* were able to successfully construct a dual gene vector like the one taught in the instant invention. Further, Gage *et al.* disclose a construct where gene expression is tetracycline driven; there is no suggestion or motivation that a heat shock promoter could be substituted for the LTR to drive the tetracycline controlled transactivator (tTA) which in turn activates transcription from the minimal Promoter P_{hCMV-1} to drive heterologous gene expression. In fact, substituting a heat shock promoter would require an entirely different expression system. The only conceivable motivation to combine the references is based on the hindsight gleaned from the instant invention. When applying obviousness rejections, the references must be viewed without the benefit of impermissible

hindsight vision afforded by the claimed invention (See MPEP 2141; Basic considerations which apply to obviousness rejections).

Furthermore, Applicants teach a method and expression construct resulting in *higher gene expression* (see comments under 102(b) section, *supra*). Applicants refer the Examiner to the attached copy of the reference entitled: "Construction of new amplifier expression vectors for high levels of IL-2 gene expression" (Tsang *et al.* 2000 International Journal of Molecular Medicine 5:295-300); this reference underscores the unprecedented high gene expression levels of the claimed constructs. Applicants state that the amplifier constructs produced 11 to 28 times more secreted IL-2 than the CMV promoter control (see abstract). The high gene expression levels of the constructs are an inherent advantage of the instant invention and provide for unexpected results. MPEP 2141 states the following:

OBJECTIVE EVIDENCE MUST BE CONSIDERED

Objective evidence or secondary considerations such as **unexpected results**, commercial success, **long-felt need**, **failure by others**, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are presented. When evidence of any these secondary considerations is submitted, the examiner must evaluate the evidence... [bold emphasis added]

In light of the above comments, Applicants respectfully request that the rejection of claims 1, 10, 12, 13, 15, 16, 39 and 44-46 under 35 U.S.C. §103(a) be withdrawn.

Claims 1, 7, 39, and 41 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bromley *et al.* taken with any one of Stover, Hickey *et al.*, Gaestel *et al.*, Dale *et al.*, or Quail *et al.*

The rejection of claims 1 and 39 is respectfully traversed.

Claims 1 and 39 have been amended (*supra*). Claims 7 and 41 have been canceled. For the same reasons as discussed above, there is no motivation to combine the references in light of the fact that Bromley *et al.* were not able to construct a dual gene vector such as the one disclosed in the instant invention at the time of filing of EP 0299127 (*supra*). Thus, Applicants respectfully request that the rejection of claims 1 and 39 under 35 U.S.C. §103(a) be withdrawn.

Claims 1, 10, 11, 39 and 44 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bromley *et al.* taken with any one of Dubensky Jr. *et al.*, Scott *et al.*, Saito *et al.*, Weinberg *et al.*, Beach *et al.*, or Tewari *et al.*

The rejection of claims 1, 10, 11, 39 and 44 is respectfully traversed.

Claims 1 and 39 have been amended (*supra*).

As already discussed, with respect to the 35 U.S.C. § 102(b) and 103(a) rejections, Bromley *et al.* were not able to construct a dual gene vector such as the one disclosed in the instant invention at the time of filing of EP 0299127 (*supra*). Thus, there is no motivation to combine the references. Applicants assert that it is clear, especially in light of the declaration submitted by Dr. Harris, that at the time the claimed invention was made, only Applicants were able to successfully construct the dual gene expression vectors. As pointed out in the declaration, Applicants were the first to publish the successful construction of a dual gene expression vector that facilitates the simultaneous expression of two genes. The Examiner opines that as expression of the claim-designated proteins by recombinant methods is clearly known in the art, one of ordinary skill would have been motivated to express these proteins in the vector of Bromley *et al.* in view of the teachings of Bromley *et*

al. that expression of the proteins using the vector can be suitably regulated by environmental conditions. Applicants assert that Bromley *et al.*, taken alone, or in combination with the secondary references could not have taught the dual gene expression vectors of the instant invention, let alone the higher gene expression levels. Since Bromley *et al.* were unable to construct the dual gene expression vector (see declaration), one of ordinary skill would not have been motivated to express the claim-designated proteins in the vector of Bromley *et al.* Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 1, 10, 11, 39 and 44 under 35 U.S.C. §103(a).

Claims 1 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bromley *et al.*, taken with any one of Loeb *et al.*, Hancock, or Talavera *et al.*

The rejection of claims 1 and 15 under 35 U.S.C. § 103(a) is respectfully traversed.

Claim 1 has been amended (*supra*).

Since Bromley *et al.* were not able to construct a dual gene vector such as the one disclosed in the instant invention at the time of filing of EP 0299127 (*supra*), there is no motivation to combine the references. As pointed out above, the only conceivable motivation to combine the references is based on the hindsight gleaned from the instant invention. The Examiner argues that it must be recognized that any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. The Examiner further argues that Bromley *et al.* clearly teach the claim-designated thermoinducible construct.

Applicants emphasize that in light of the declaration submitted by Dr. Harris it has clearly been established that Bromley *et al.* could not have taught the claim-designated thermoinducible construct. At the time the claimed invention was made, only Applicants were able to successfully construct the dual gene expression vectors. Moreover, it is known to Applicants that even 10 years after Bromley *et al.* had filed their PCT application they had not yet constructed a single dual gene vector as disclosed in the instant invention. In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1 and 15 under 35 U.S.C. § 103(a).

Table 4

Some of the numbers recorded in Table 4 are incorrect. Due to an unintentional error, the numbers were incorrectly submitted in the original patent application. Applicants request that the corrected numbers be entered. The corrected numbers are supported by the specification as filed. No new matter has been added. The corrected numbers are **14.28** for L-27 in column 1 (37°C); **78.40** for F12 in column 1 (37°C); **106.88** for F12 in column 2 (39°C); **149.93** for F12 in column 3 (41°C); **230.02** for F12 in column 4 (42°C); and **188.13** for F12 in column 5 (44°C). Entry of the amendment is respectfully requested.

Sequence Compliance

Applicants wish to apologize to the Examiner for a misinterpretation of the Examiner's suggestion with respect to the sequence compliance of Figure 10 in the specification. Applicants previous arguments with respect to sequence compliance are

withdrawn. According to the Examiner, reference must be made to the sequence disclosed in Figure 10, either in the figure or in the text of the description of the figure, by use of the sequence identifier, preceded by "SEQ ID NO.". The specification has been amended to comply with the requirements of 37 C.F.R. §1.821(d) and a sequence identifier (SEQ ID NO:1) has been added to the paragraph referring to Figure 10 in the "Brief Description of the Drawings". Entry of this amendment is respectfully requested.

Conclusion

Reconsideration of claims 1, 5, 9-18, 20-26, 33, 35-39 and 43-46 in view of the foregoing amendments and remarks, and an early indication of their allowability, are earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at line 4 of page 12 has been amended as follows:

Fig. 10 shows the DNA sequence (SEQ ID NO:1) of the BamHI-HindIII fragment of p173OR from StressGen Biotechnology Corp. This fragment contains the approximately 0.4kb minimal HSP70B promoter fragment used in constructs of the specific examples, Example 1 and 3, below.

Paragraph beginning at line 1 of page 66 (Table 4) has been amended as follows:

TABLE 4

	I.U. of IL-2				
temperature:	37°C	39°C	41°C	42°C	44°C
heat shock duration:	continuous	continuous	1 hr	1hr	0.5 hr
Lipid alone	2.03	0.50	0.41	0.53	0.53
L-27	14.28	9.88	5.95	9.88	7.80
007	336.76	318.49	334.02	373.74	389.27
F12	78.40	106.88	149.93	[60.02] 230.02	188.13
C8	9.19	8.03	11.74	8.73	16.37

IN THE CLAIMS:

Claims 6, 7 and 41 have been canceled.

Claim 1 has been amended as follows:

1. (Twice Amended) A method of effecting expression of a selected polynucleotide in a mammalian cell comprising:

- (a) providing an expression construct, said expression construct comprising (i) a heat shock promoter selected from the group consisting of HSP70, HSP90, HSP60, HSP27, HSP25, and ubiquitin promoters, operably linked to a gene encoding a transactivating factor; and (ii) a second promoter operably linked to said selected polynucleotide, wherein said second promoter is activated by said transactivating factor;
- (b) introducing said expression construct into said cell; and
- (c) subjecting said cell to hyperthermic conditions [comprising a temperature between about 37°C and about 42°C] which activate said heat shock promoter, wherein said conditions result in the expression of said selected polynucleotide.

Claim 9 has been amended as follows:

- 9. (Amended) The method of claim 1, wherein said second promoter is selected from the group consisting of an HIV-1 promoter and an HIV-2 promoter [, and said transactivating factor is tat].

Claim 18 has been amended as follows:

- 18. (Twice Amended) A method of providing a subject with a therapeutically effective amount of an expression product of a selected polynucleotide comprising:
 - (a) providing [a first] an expression construct, said expression construct comprising (i) a heat shock promoter selected from the group consisting of HSP70, HSP90, HSP60, HSP27, HSP25, and ubiquitin promoters, operably linked to a gene encoding a transactivating factor; and (ii) a second promoter operably linked to said selected polynucleotide, wherein said second promoter is activated by said transactivating factor;
 - [(b) providing a second expression construct, said second expression construct comprising a second promoter operably linked to said selected

polynucleotide, wherein said second promoter is activated by said transactivating factor;]

[(c)] (b) introducing said [first and second] expression construct into a cell of said subject; and

[(d)] (c) subjecting said cell to hyperthermic conditions [comprising a temperature between about 37°C and about 42°C] which activate said heat shock promoter, wherein expression of said selected polynucleotide is induced by said hyperthermic conditions.

Claim 33 has been amended as follows:

33. (Twice Amended) A method for provoking an immune response in a mammal comprising:

- (a) providing an expression construct, said expression construct comprising (i) a heat shock promoter selected from the group consisting of HSP70, HSP90, HSP60, HSP27, HSP25, and ubiquitin promoters, operably linked to a gene encoding a transactivating factor; and (ii) a second promoter operably linked to a selected polynucleotide, wherein said second promoter is activated by said transactivating factor;
- (b) introducing said expression construct into a cell in the mammal; and
- (c) subjecting said cell to hyperthermic conditions [comprising a temperature between about 37°C and about 42°C] which activate said heat shock promoter, wherein said hyperthermic conditions result in the expression of said selected polynucleotide and the expression product of the selected polynucleotide is expressed in an amount effective to provoke an immune response in said mammal, said immune response being selected from the group consisting of a humoral immune response and a cellular immune response.

Claim 38 has been amended as follows:

38. (Twice Amended) A method of altering the genetic material of a mammal, comprising:
- (a) providing an expression construct, said expression construct comprising (i) a heat shock promoter selected from the group consisting of HSP70, HSP90, HSP60, HSP27, HSP25, and ubiquitin promoters, operably linked to a gene encoding a transactivating factor; and (ii) a second promoter operably linked to a selected polynucleotide, wherein said second promoter is activated by said transactivating factor; and
 - (b) introducing said expression construct into a cell of said mammal.

Claim 39 has been amended as follows:

39. (Twice Amended) An expression construct comprising:
- (a) a gene encoding a transactivating factor;
 - (b) a heat shock promoter selected from the group consisting of HSP70, HSP90, HSP60, HSP27, HSP25, and ubiquitin promoters, operably linked to said gene, wherein said heat shock promoter is activated at hyperthermic conditions [comprising a temperature between about 37°C and about 42°C];
 - (c) a selected polynucleotide; and
 - (d) a second promoter operably linked to said selected polynucleotide, said second promoter being activated by said transactivating factor.

Claim 47 has been added.

47. (New) The method of claim 1, wherein said transactivating factor is tat.